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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,753	08/08/2006	Jonathan Cebon	029860-0145	3988

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,753	CEBON ET AL.	
	Examiner	Art Unit	
	MARIANNE DIBRINO	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-22,25,26 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-22, 25, 26, 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/13/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 11/13/09 is acknowledged and has been entered.

2. Applicant' is reminded of Applicant's election of Group III (claims 20-27) and species of ISCOMATRIX as the saponin-based adjuvant comprising a sterol in Applicant's amendment filed 3/19/09.

Claims 20-22, 25, 26 and 35-37 read on the elected species.

Upon consideration of the art, examination has been extended to the species recited in instant claim 34.

Claims 20-22, 25, 26 and 34-37 and are presently being examined.

3. Applicant's amendment filed 11/13/09 has overcome the prior rejection of record of claims 20-27 under 35 U.S.C. 112, first paragraph, scope of enablement.

4. Applicant's amendment filed 11/13/09 has overcome the prior rejection of record of claim 24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 20-22, 25, 26, 34 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Cebon *et al* ((Proc. Amer. Soc. Clin. Oncol. 21: 6/2002, abstract 86 and presentation slides, of record) and an admission in the specification at [0022].

Claims 20-27 were rejected upon the basis set forth below in the prior Office Action of record. Applicant's amendment filed 11/13/09 has necessitated the rejection set forth below (*i.e.,* the cancellation of claims 23, 24 and 27, amendment of the pending claims, and the addition of claims 35-37).

Cebon *et al* teach administering a composition comprising full length NY-ESO-1 protein and ISCOM adjuvant intramuscularly to patients with NY-ESO-1 positive tumors (tumors determined by immunohistochemistry or RT-PCR) but with minimal residual disease, in order to evaluate the safety and immunogenicity of the composition and to correlate clinical response, wherein the amount of NY-ESO-1 protein is 10, 30 or 100 ug. Cebon *et al* teach that ISCOMs are saponin-based adjuvants known to stimulate antibody

responses and induce T helper cell (CD4+) and cytotoxic T lymphocyte (CD8+) responses in a variety of animal models and human clinical trials. Cebon *et al* teach intramuscular administration of their composition.

The admission in the specification at [0022] is that eligible subjects for evaluation of relapse risk were defined as those who had exhibited a cancer that expressed NY-ESO-1 as determined by either immunohistochemistry or RT-PCR, and had minimal residual disease, the same patient population taught by Cebon *et al*.

Although Cebon *et al* do not explicitly teach the amount of ISCOM administered, Cebon *et al* teach that the control amount of ISCOM administered was 100 ug. Therefore, it appears that the amount of ISCOM in the composition with NY-ESO-1 at least for the 100 ug NY-ESO-1 administration is equal in amount. Although Cebon *et al* do not correlate the clinical response in their study, immunization resulted in both humoral and cellular responses. In addition, the protocol used by Cebon *et al* is the same as that disclosed in the instant specification. Thus, it appears that the limitation "A method for reducing the risk of relapse in a subject at risk of a relapse of a cancer, cells of which express NY-EOS-1" recited in instant base claim 20 is met by the art reference. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show a distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on pages 5-7.

Applicant argues that Cebon does not teach or suggest methods of reducing the risk of relapse, nor that a composition comprising NY-ESO-1 protein and a saponin-based adjuvant could or should be used to reduce the risk of relapse, nor does Cebon contemplate administration of said composition to subjects at risk of relapse of a cancer which cells express NY-ESO-1.

However, the admission in the specification at [0022] concerning the patient population evaluated for risk of relapse matches the art reference teaching of the patient population, and the art-taught protocol is the same protocol as Applicant's protocol (see Example 6 in the specification, for example), as enunciated supra. Thus, although Cebon *et al* do not explicitly teach that administration of the composition reduces the risk of relapse, it appears to be an inherent property of the art method that it reduces the risk of relapse, as enunciated supra.

It does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). "{i}t is a general rule that merely discovering and claiming a new benefit of an old process cannot render the process again patentable." In re Woodruff, 16 USPQ2d 1934, 1936 (Fed. Cir. 1990). The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

With regard to Applicant's further arguments about unexpected results, "Evidence of secondary considerations, such as unexpected results or commercial success, is irrelevant to 35 U.S.C. 102 rejections and thus cannot overcome a rejection so based. *In re Wiggins*, 488 F.2d 538, 543, 179 USPQ 421, 425 (CCPA 1973)." See MPEP 2131.04

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 20-22, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/14464 (IDS reference filed 11/13/09) in view of Batchu *et al* (Human Gene Therapy, 9/03, 14(14): 1333-1345) and WO 03/076455 A2 (9/18/03, IDS reference filed 11/13/09).

WO 98/14464 teaches administering NY-ESO-1 protein in a saponin-based adjuvant to a patient with a NY-ESO-1-expressing tumor for treatment such as for treatment of breast cancer or melanoma. WO 98/14464 also teaches studying the progression and regression of cancer, and that both antibody (*i.e.,* and CD4+ T cell help for antibody production) and CTL (*i.e.,* CD8+ T cell) responses are elicited (see entire reference, especially page 19 starting at the first full paragraph, page 20 and lines 1-5 of page 21, claims 24-26, 72, Tables 3-4).

WO 98/14464 does not teach that the treatment method comprising administering NY-ESO-1 protein in a saponin based adjuvant comprises a method for reducing the risk of relapse in a subject, nor does it teach the route of administration, or that the saponin based adjuvant is an ISCOM or an ISCOMATRIX.

Batchu *et al* teach that NY-ESO-1 has been identified in melanoma, breast tumors, prostate cancers, neuroblastomas, and to various degrees in lung, bladder, hepatocellular, ovarian and thyroid cancers as well as in advanced stages of myeloma. Batchu *et al* further teach that NY-ESO-1/adjuvant based therapies (including NY-ESO-1-transduced DCs) can be used for treatment or to reduce the risk of relapse in patients by eradicating residual tumor cells, and that antibody, CD4+ and CD8+ T cell responses can all be produced to NY-ESO-1 protein (see entire reference, especially page 1334 at column 1 at the second full paragraph, discussion section at the first three paragraphs and the last paragraph).

WO 03/076455 A2 teaches that saponin based adjuvants include ISCOMs and ISCOMATRIX and that therapeutic compositions may be administered by such routes as intramuscular or subcutaneous (especially paragraph spanning pages 35-36 and [0096]).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the method of administering the composition taught by WO 98/14464 for reducing the risk of relapse of cancer patients such as taught is desirable to do by Batchu *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this to eradicate residual cancer cells as taught by Batchu *et al*.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the composition intramuscularly or subcutaneously as taught by WO 03/076455 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because they are common routes of administration of therapeutic proteins as taught by WO 03/076455 A2.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the ISCOM or ISCOMATRIX adjuvants taught by WO 03/076455 A2 as the saponin-based adjuvant in the composition taught by WO 98/14464.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because they are both saponin-based adjuvants and WO 98/14464 does not specify what the particular saponin-based adjuvant is.

9. Claims 25, 26, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/14464 (IDS reference filed 11/13/09) in view of Batchu *et al* (Human Gene Therapy, 9/03, 14(14): 1333-1345) and WO 03/076455 A2 (9/18/03, IDS reference filed 11/13/09) as applied to claims 20-22, 34 and 35 above, and further in view of Jager *et al* (PNAS 2000, 97(22): 12198-12203) and US 6,506,386 B1.

The combination of WO 98/14464, Batchu *et al* and WO 03/076455 A2 have been discussed supra, hereafter referred to as "the combined references."

The combined references do not teach wherein the amount of protein administered is about 10 to about 500 ug, nor about 100 ug, nor that the composition comprising the protein and adjuvant is administered via an intradermal route, nor that equal amounts of protein and saponin based adjuvant are administered to the subject.

Jager *et al* teach that NY-ESO-1 is a highly immunogenic cancer-testis antigen, inducing simultaneous cellular and humoral immune responses in a high percentage of patients with advanced NY-ESO-1-expressing tumors. Jager *et al* further teach administration of NY-ESO-1 CTL epitope peptides via an intradermal route of administration using 100 ug of each peptide. Jager *et al* teach monitoring disease stabilization (see entire reference, especially abstract, introduction and materials and methods sections).

US 6,506,386 B1 discloses that vaccine compositions may be formulated to contain an ISCOM saponin-based adjuvant and an antigenic protein, the antigenic protein being present at a range of 1 to 1000 ug, including a range of 1-100 ug of protein. US 6,506,386 B1 discloses that the saponin will typically be present for human administration in the range of 1 to 100 ug per dose, and that the adjuvants of the invention are suitable for administration via any route (see entire reference, especially column 1 at lines 5-12, column 5 at lines 28-33 and lines 57-64, column 6 at lines 3-5, and column 8 at lines 53-63).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have formulated the composition of the combined references to contain equal amounts of NY-ESO-1 protein and ISCOM adjuvant, for example, 100 ug of each, and to have administered it via an intradermal route.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this because the combined references do not specify what amounts of protein and adjuvant are used, while US 6,506,386 B1 discloses using up to about 100 ug of saponin-based adjuvant per dose and also discloses using protein at 100 ug, and Jager *et al* also teach using 100 ug of antigen. One of ordinary skill in the art at the time the invention was made would have been motivated to administer the composition intradermally because Jager *et al* teach intradermal administration of NY-ESO-1

antigenic peptides and because US 6,506,386 B1 discloses that any route of administration is suitable.

10. Claims 20-22, 25, 26 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cebon *et al* ((Proc. Amer. Soc. Clin. Oncol. 21: 6/2002, abstract 86 and presentation slides, of record) in view of Jager *et al* (PNAS 2000, 97(22): 12198-12203), WO 03/076455 A2 (9/18/03, IDS reference filed 11/13/09) and an admission in the specification at [0022].

Applicant's amendment filed 11/13/09 has necessitated the new ground of rejection set forth below

Cebon *et al* teach administering a composition comprising full length NY-ESO-1 protein and ISCOM adjuvant intramuscularly to patients with NY-ESO-1 positive tumors (tumors determined by immunohistochemistry or RT-PCR) but with minimal residual disease, in order to evaluate the safety and immunogenicity of the composition and to correlate clinical response, wherein the amount of NY-ESO-1 protein at 10, 30 or 100 ug. Cebon *et al* teach that ISCOMs are saponin-based adjuvants known to stimulate antibody responses and induce T helper cell (CD4+) and cytotoxic T lymphocyte (CD8+) responses in a variety of animal models and human clinical trials. Cebon *et al* teach intramuscular administration of their composition.

Cebon *et al* do not teach that the composition comprises ISCOMATRIX rather than ISCOM and that administration may be by an intradermal route.

Jager *et al* teach that NY-ESO-1 is a highly immunogenic cancer-testids antigen, inducing simultaneous cellular and humoral immune responses in a high percentage of patients with advanced NY-ESO-1-expressing tumors. Jager *et al* further teach administration of NY-ESO-1 CTL epitope peptides via an intradermal route of administration using 100 ug of each peptide. Jager *et al* teach monitoring disease stabilization (see entire reference, especially abstract, introduction and materials and methods sections).

WO 03/076455 A2 teaches that saponin based adjuvants include ISCOMs and ISCOMATRIX and that therapeutic compositions may be administered by such routes as intramuscular or subcutaneous (especially paragraph spanning pages 35-36 and [0096]).

The admission in the specification at [0022] is that eligible subjects for evaluation of relapse risk were defined as those who had exhibited a cancer that expressed NY-ESO-1 as determined by either immunohistochemistry or RT-PCR, and had minimal residual disease, the same patient population taught by Cebon *et al*.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used any equivalent saponin-based adjuvant in the composition taught by Cebon *et al* and any effective art known delivery route for the composition.

One of ordinary skill in the art at the time the invention was made would have been motivated to pursue the known options within is or her technical grasp in order to investigate optimization of NY-ESO-1 delivery.

Although Cebon *et al* do not explicitly teach the amount of ISCOM administered, Cebon *et al* teach that the control amount of ISCOM administered was 100 ug. Therefore, it appears that the amount of ISCOM in the composition with NY-ESO-1 at least for the 100 ug NY-ESO-1 administration is equal in amount. Although Cebon *et al* do not correlate the clinical response in their study, immunization resulted in both humoral and cellular responses. In addition, the protocol used by Cebon *et al* is the same as that disclosed in the instant specification. Although Cebon *et al* do not explicitly teach that administration of the composition reduces the risk of relapse, it is an expected property of the art method that it reduces the risk of relapse. Thus, it appears that the limitation "A method for reducing the risk of relapse in a subject at risk of a relapse of a cancer, cells of which express NY-EOS-1" recited in instant base claim 20 is met by the art reference. Therefore, the claimed process appears to be similar to the process of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Applicant's arguments have been fully considered but are not persuasive.

Applicant's arguments are of record in the said amendment on pages 5-7 with regard to Cebon *et al* and to unexpected results.

Applicant argues that Cebon does not teach or suggest methods of reducing the risk of relapse, nor that a composition comprising NY-ESO-1 protein and a saponin-based adjuvant could or should be used to reduce the risk of relapse, nor does Cebon contemplate administration of said composition to subjects at risk of relapse of a cancer which cell express NY-ESO-1.

However, the admission in the specification at [0022] concerning the patient population evaluated for risk of relapse matches the art reference teaching of the patient population, and the art-taught protocol is the same protocol as Applicant's protocol, as enunciated supra. Thus, although Cebon *et al* do not explicitly teach

that administration of the composition reduces the risk of relapse, it is an expected property of the art method that it reduces the risk of relapse, as enunciated supra.

With regard to Applicant's further arguments about unexpected results, the following applies. Applicant argues relapse rates of patients who are administered a composition comprising NY-ESO-1 protein and ISCOM adjuvant *vs* patients administered the NY-ESO-1 protein alone without ISCOM adjuvant, and study time up to about 3 years. Applicant also presents evidence in the form of a manuscript by Nicholaou *et al* with Inventors Chen, Davis and Cebon among the co-authors, said manuscript teaching relapse-free survival three years post-vaccination in 10/14 patients receiving the composition comprising NY-ESO-1 protein and ISCOMATRIX adjuvant as compared with those receiving NY-ESO-1 alone or placebo. Applicant further argues that there is no teaching or suggestion in Cebon *et al* of a method of preventing relapse, no indication that the claimed methods would achieve such dramatic, beneficial results in the context of preventing relapse, and that the results reported in the instant application and in Nicholaou are evidence of unexpected results that further support patentability.

First, the claims do not recite that the method prevents relapse as alleged by Applicant; rather, the claims recite that the method reduces the risk of relapse. Second, as enunciated supra, the protocol is the same protocol as Applicant's protocol, and as evidenced by the specification, the protocol reduces the risk of relapse. Applicant's evidence is directed at the difference in relapse between patients administered the composition containing the protein and adjuvant *vs* just the protein alone. Likewise, Cebon *et al* teach administering both the protein and adjuvant or just the protein alone. The instant claims do not recite that the risk of relapse is reduced for a defined amount of time.

11. Claim 20 is objected to because of the following informality: claim 20 appears to contain a grammatical error, *i.e.*, "cells" at line 2 should be "the cells". Appropriate correction is required.

12. No claim is allowed.

13. Applicant's amendment and IDS, both filed 11/13/09, have necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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